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Cigarette Smoking and Risk of Stroke in the Chinese Adult Population

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Abstract

Background and Purpose—We studied the relationship between cigarette smoking and stroke incidence and mortality in the Chinese adult population.

Methods—We conducted a prospective cohort study in a nationally representative sample of 169,871 Chinese men and women aged 40 years and older. Data on cigarette smoking and other covariables were collected at a baseline examination in 1991 using a standard protocol. Follow-up evaluation was conducted in 1999-2000, with a response rate of 93.4%.

Results—During an average of 8.3 years follow-up, a total of 6,780 stroke events (3,979 fatal strokes) were observed. The multivariate-adjusted relative risks (95% confidence interval) of stroke incidence and mortality associated with current cigarette smoking were 1.28 (1.19-1.37) and 1.13 (1.03-1.25) in men and 1.25 (1.13-1.37) and 1.19 (1.04-1.36) in women, respectively. The corresponding population attributable risks were 14.2% and 7.1% in men and 3.1% and 2.4% in women. Compared to never-smokers, the multivariate-adjusted relative risks of stroke incidence (95% confidence interval) were 1.21 (1.12-1.31), 1.21 (1.11-1.32), and 1.36 (1.25-1.47) for those who smoked 1-9, 10-19, and ≥20 cigarettes per day; and 1.18 (1.09-1.28), 1.25 (1.15-1.35), and 1.34 (1.24-1.44) for those who smoked 1-11, 12-26, and >26 pack-years, respectively (both $p < 0.0001$ for linear trends).

Conclusions—Our study identified a positive and dose-response relationship between cigarette smoking and risk of stroke. Smoking prevention and cessation programs should be an important strategy for reducing the burden of stroke in Chinese adults.

Keywords

smoking; stroke; relative risk; Chinese

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Disclosure

We declare that we have no conflict of interest related to this work.

Data Access and Responsibility

Tanika Kelly, Dongfeng Gu, and Jiang He had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Stroke is the second leading cause of deaths and the leading cause of long-term disability worldwide (1). In 2005, stroke caused an estimated 5.7 million deaths and 87% of these deaths were in low-income and middle-income countries (2). Without intervention, the number of global stroke deaths is projected to rise to 6.5 million in 2015 and to 7.8 million in 2030, and the majority of these deaths will be borne by low-income and middle-income countries, especially by China (2).

Cigarette smoking is an important risk factor for all-cause mortality as well as vascular disease mortality (1,3). Many prospective cohort studies conducted in western populations have indicated a strong and independent relationship between cigarette smoking and risk of stroke (4,5). However, this relationship has not been well established in Asian populations (6,7). With a population of 1.3 billion, China is the world's largest producer and consumer of tobacco (8). Establishing the association between cigarette smoking and risk of stroke in the Chinese population will enable the development of an effective prevention strategy aimed at reducing stroke-related mortality and disability burden in China.

The purpose of the current study was to examine the relationship between cigarette smoking and stroke incidence and mortality in a large, population-based prospective cohort of Chinese adults. In addition, this study investigated the dose-response and gender-specific effects of cigarette smoking on the risk of stroke.

MATERIALS AND METHODS

Study Population

In 1991, the third China National Hypertension Survey was carried out in all 30 provinces of mainland China using a multi-stage random cluster sampling design to select a nationally representative sample of Chinese adults aged 15 years or older (9). In 1999-2000, investigators from each province were invited to participate in follow-up study. Of the 30 provinces, 13 were not included in the follow-up study because study participants' contact information was not available. Overall, 83,533 men and 86,338 women aged 40 years or older at their baseline examination were eligible to participate in the follow-up study. From this population, a total of 158,666 (93.4%) study participants (or their proxies) were identified and interviewed as part of the follow-up study. In this report, study participants missing information on cigarette smoking status (n=14,578) were excluded from all analyses, and those with prevalent stroke (n=2,291) were excluded from the analysis of stroke incidence. Participants included in the final analysis were not different from the overall study population in 1991 regarding their baseline characteristics.

Baseline Examination

Baseline data were collected at a single clinic visit by specially trained physicians and nurses using standardized methods with stringent levels of quality control (9). Data on demographic characteristics, medical history, and lifestyle risk factors were obtained using a standard questionnaire administered by trained staff. Cigarette smoking was defined as having smoked at least 1 cigarette per day for 1 year or more. For participants that reported past or current cigarette smoking, information on the number of cigarettes smoked per day along with the duration of cigarette smoking was also collected. Work-related physical activity was assessed because leisure-time physical activity was uncommon. Alcohol consumption was defined as drinking alcohol at least 12 times during the last year. Body weight and height were measured in light indoor clothing without shoes according to a standardized protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Three blood pressure (BP) measurements were taken after the study participant had been seated quietly for

5 minutes using a standard mercury sphygmomanometer according to a standard protocol (10). The mean of 3 systolic BP (SBP) measures was used in all analyses.

Follow-up Data Collection

The follow-up examination, which was conducted between 1999 and 2000, included tracking study participants or their proxies to a current address, performing in-depth interviews to ascertain disease status and vital information, and obtaining hospital records and death certificates. If a study participant reported a hospitalization or emergency room overnight-stay due to stroke during the in-person interview, participant's hospital records, including medical history, physical examination findings, laboratory test results, CT scan, MRI, discharge diagnosis, and/or autopsy reports were abstracted by trained staff using a standard form. All deaths reported during the in-person interview were verified by obtaining death certificates from the local public health department or police department. If death occurred during a hospitalization, the participant's hospital records and autopsy results were also abstracted by trained staff using a standard form. If death occurred outside of the hospital, detailed information on medical history was obtained from a family member or healthcare provider. An end-point assessment committee within each province reviewed all abstracted information to confirm or reject the occurrence of study outcomes using pre-established criteria (11).

A study-wide end point assessment committee at the Chinese Academy of Medical Sciences in Beijing, China reviewed all hospital records and death certificates and determined the final diagnosis of event or the underlying cause of death. Two committee members independently verified the diagnosis and discrepancies were adjudicated by discussion involving additional committee members. All members of the local and study-wide end point assessment committees were blinded to the study participant's baseline risk factor information. Causes of death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). For this analysis, stroke incidence was defined as a confirmed diagnosis of stroke during the follow-up period or stroke listed as an underlying cause of death (ICD-9 430.0-438.9) among those without a history of stroke. Stroke mortality was defined as stroke listed as an underlying cause of death among all study participants. Of the 6,780 stroke events CT or MRI imaging was available for 4,430 (65.3%) stroke cases.

This study was approved by the Tulane University Health Sciences Center Institutional Review Board and the Cardiovascular Institute and Fu Wai Hospital Ethics Committee. Written informed consent was obtained from all study participants at their follow-up visit.

Statistical Analysis

Baseline characteristics were compared between current and former smokers and never-smokers using X^2 tests for categorical variables and ANOVA for continuous variables. Person-years of follow-up were calculated from the date of baseline examination until the date of stroke, death, or follow-up interview for each study participant. Age-standardized incidence and mortality were calculated using the 5-year age-specific incidence and mortality and the age distribution of the Chinese population from year 2000 census data.

Cox proportional hazards regression models were used to examine the association between smoking and stroke adjusted for baseline age, sex, education, alcohol consumption, physical activity, SBP, BMI, geographic region (north vs. south), urbanization (rural vs. urban), baseline cardiovascular disease (CVD), and the prevalence of diabetes at baseline as well as new onset diabetes during follow-up. Multivariate-adjusted relative risks were calculated using never-smokers as the reference category. The population attributable risks (PAR), measured as the percentage of stroke events or deaths that could be prevented if current cigarette smoking was eliminated in the population, were calculated. Dose-response relationships for current smokers

were investigated using never-smokers as the reference group compared to three levels of daily cigarettes smoked (1-9, 10-19, and ≥ 20 cigarettes per day) and tertiles of pack-years (1-11, 12-26, and >26 pack-years). Sub-group analyses by gender and stroke subtype were also conducted. Methods to estimate variances that take into account sample clustering were used in Cox proportional hazards models (12). Statistical analyses were conducted using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

Baseline characteristics of study participants are presented in Table 1. Overall, 62.1% of study participants were never-smokers, 2.3% were former smokers, and 35.6% were current smokers, with the prevalence of current cigarette smoking higher in men compared to women (59.1% versus 13.0%).

During an average of 8.3 years follow-up we documented a total of 6,780 stroke events, including 3,979 stroke deaths. After adjustment for important covariables, current cigarette smoking remained a significant predictor of stroke incidence and mortality in the overall and gender-specific analyses (Table 2). The PAR due to current cigarette smoking was 8.2% (95% CI 5.8%-10.8%) of incident strokes and 4.8% (95% CI 1.5%-8.0%) of stroke deaths in the total population. PAR estimates were higher for men than women, with current smoking accounting for 14.2% (95% CI 9.2%-18.6%) of stroke events and 7.1% (95% CI 1.0%-13.5%) of stroke deaths in men compared to 3.1% (95% CI 1.4%-4.9%) of stroke events and 2.4% (95% CI 0.3%-4.9%) of stroke deaths in women.

Tables 3 and 4 present relative risks of stroke incidence and mortality in current compared to never-smokers according to the number of cigarettes smoked per day and pack-years smoked, respectively. There was a significant and linear association between both the number of cigarettes smoked per day and pack-years smoked and stroke incidence in the overall and gender-specific analyses (all p-values for linear trends <0.01). Although current smoking was associated with an increased risk of stroke mortality, the association did not seem to be in a dose-response fashion.

In addition, we conducted analyses by subtype of stroke. Of the 6,780 confirmed stroke events, 3,409 (50.3%) were classified as ischemic, including 1,097 fatal ischemic strokes, 2,353 (34.7%) were classified as hemorrhagic, including 2,002 fatal hemorrhagic strokes, 950 (14.0%) were of unknown subtype (not classified as either ischemic or hemorrhagic), and 68 were classified as both ischemic and hemorrhagic subtypes. Those classified as both were removed from the subtype analysis. There was a strong and graded association between cigarette smoking and risk of ischemic stroke. Compared to never-smokers, the multivariate-adjusted relative risks of ischemic stroke (95% CI) were 1.25 (1.12-1.40), 1.31 (1.17-1.47), and 1.51 (1.36-1.67) for those who smoked 1-9, 10-19, and ≥20 cigarettes per day; and 1.19 (1.05-1.34), 1.36 (1.22-1.52), and 1.47 (1.32-1.62) for those who smoked 1-11, 12-26, and >26 pack-years, respectively (both p <0.0001 for linear trends). A positive association between cigarette smoking and hemorrhagic stroke was also observed, with corresponding relative risks of 1.19 (1.05-1.36), 1.14 (0.98-1.32), and 1.20 (1.04-1.37) for those who smoked 1-9, 10-19, and ≥20 cigarettes per day; and 1.20 (1.05-1.37), 1.17 (1.01-1.35), and 1.18 (1.03-1.35) for those who smoked 1-11, 12-26, and >26 pack-years, respectively (both p-values for linear trends = 0.007).

DISCUSSION

This study documents an independent and dose-response relationship between cigarette smoking and stroke incidence in a large, nationally representative sample of the Chinese adult

population. A significantly elevated risk of stroke mortality was also observed among current compared to never-smokers, although evidence for a linear relationship between smoking and stroke mortality was less clear. These results were consistent among men and women and highlight cigarette smoking as an independent risk factor for stroke in Chinese adults. In addition, these findings indicate that prevention and cessation of cigarette smoking could reduce stroke morbidity and mortality by 8.2% and 4.7%, respectively, in the Chinese adult population.

Our study has several important strengths. It is the first large prospective cohort examining the association between cigarette smoking and risk of stroke in a population-based, nationally representative sample of Chinese adults. Information on baseline cigarette smoking, other co-variables, and stroke outcomes were assessed using stringent quality control procedures and a very high follow-up rate was attained. Our study also has certain limitations. Information on cigarette smoking was not collected in two provinces. Therefore, a relatively large number of study participants are missing information on cigarette smoking. However, it is unlikely that this type of missing information will bias the reported association in our study. In addition, data on cigarette smoking was collected only at the baseline examination, and therefore, changes in smoking status over the follow-up period could not be assessed. Moreover, data on serum lipids, diet, and leisure time physical activity were not obtained. Lack of adjustment for these variables may have resulted in a slight over-estimate of the relative risk of stroke.

While a positive association between cigarette smoking and stroke incidence and mortality have been established in western populations, with relative risks of stroke ranging from 1.33 to 2.50 for current compared to never smokers (4,5,13,14), contradictory findings have been reported in Asian cohorts (6,15,16). Our study found a significantly increased risk of stroke incidence and mortality associated with current cigarette smoking, which has also been observed in other Japanese and Chinese populations (16-18). A recent study involving more than 500,000 participants from the Asia-Pacific region identified a 32% increased for stroke in current compared to never smokers, which was similar to our observation (7). In addition, our study identified a dose-response relationship between current cigarette smoking and stroke incidence. These results were consistent when considering both cigarettes smoked per day and pack-years smoked and in gender-subgroup and stroke subtype analyses. The dose-response relationship was also reported in prospective studies conducted in Western populations (4,5), in a Japanese cohort, and in Chinese patients with isolated systolic hypertension (7,17,18).

Our study did not find strong evidence for a dose-response relationship between cigarette smoking and stroke mortality, despite a significantly increased risk of stroke death among current compared to never-smokers. Similar results were reported from two cohort studies conducted in Shanghai, China (6,15). In contrast, studies conducted in Western populations have identified significant positive, linear relationships between smoking and stroke deaths (5,19,20). These differences could reflect true heterogeneity between populations. For example, hemorrhagic stroke accounts for less than 20% of all strokes in western populations (21). However, approximately 30-40% of incident strokes and 50% of stroke deaths were hemorrhagic in the Chinese population (22). In the current study, hemorrhagic strokes accounted for only 34.7% of incident stroke cases but made up 50.3% of all stroke deaths, and a stronger dose-response relationship between cigarette smoking and ischemic compared to hemorrhagic stroke was observed.

Some studies have identified a stronger association between cigarette smoking and the risk of stroke in women compared to men (23,24). Conversely, gender subgroup analyses presented here indicate that the risk of stroke associated with cigarette smoking is consistent across genders, which are similar to results reported elsewhere (7,19). Despite the similar relative risks of cigarette smoking between genders, we found that cigarette smoking was responsible

for approximately 14.2% of strokes in men compared to only 3.1% of strokes in women, which is consistent with past findings (25). This difference is attributed to the much higher prevalence of cigarette smoking in men than women (59.1% versus 13.0%, respectively).

In conclusion, these findings indicate an independent and graded association between cigarette smoking and the risk of stroke in Chinese men and women. These results, combined with the large stroke burden and high prevalence of cigarette smoking in China, highlight the importance of smoking prevention and cessation programs. Implementation of such public health initiatives might be a vital component for reducing stroke morbidity and mortality in Chinese adults.

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Table 1

Baseline characteristics of study participants by smoking status

Characteristics	Men			Women		
	Never-Smokers	Former Smokers	Current Smokers	Never-Smokers	Former Smokers	Current Smokers
No. of participants	28191	2965	44978	68198	568	10231
Age, mean (SD), yrs	57.3 (11.1)	60.9 (10.3)**	54.2 (9.9)**	55.7 (11.0)	64.2 (9.9)**	59.3 (9.5)**
≥High school education, %	38.8	29.8**	26.4**	18.5	5.3**	9.7**
Alcohol consumption, %	19.1	36.3**	49.0**	1.8	7.6**	9.2**
Physical inactivity, %	46.9	67.1**	32.7**	34.2	43.7**	38.9**
BMI, mean (SD), kg/m^2	23.1 (3.5)	22.6 (3.7)**	22.0 (3.2)**	22.8 (3.9)	22.9 (4.7)	22.4 (4.2)**
Systolic BP, mean (SD), mmHg	128.4 (21.4)	132.1 (23.9)**	125.2 (20.6)**	126.7 (23.9)	136.1 (28.0)**	129.6 (24.4)**
Diastolic BP, mean (SD), mmHg	79.9 (12.0)	79.2 (13.1)*	78.1 (12.0)**	76.5 (12.2)	76.7 (14.2)	77.1 (12.7)**
Diabetes, %	2.7	3.2	1.6**	2.1	4.0*	2.5*
Cardiovascular disease, %	4.3	8.5**	2.5**	2.6	6.7**	4.6**
North, %	70.6	50.8**	66.2**	61.3	60.0	82.7**
Urban, %	72.6	73.3	57.2**	58.2	66.6**	63.2**

SD = Standard deviation

* P<0.01

** P<0.0001 for X^2 test or ANOVA, compared with never-smokers.

Table 2

Relative risk of stroke by smoking status and gender

	Stroke Incidence			Stroke Mortality		
	Never	**Former**	**Current**	**Never**	**Former**	**Current**
			Total			
Person-years of follow-up (per 100,000)	677210	22139	389707	692239	23606	399572
Number of events	3788	190	2802	2285	156	1538
Age-standardized rate per 100,000 person-years	445.1	470.7	622.9	257.1	335.7	344.1
Age and sex adjusted RR (95% CI)	1.00	1.13 (0.97-1.31)	1.22 (1.16-1.29)	1.00	1.25 (1.05-1.47)	1.17 (1.09-1.25)
Multivariate adjusted RR* (95% CI)	1.00	1.03 (0.89-1.20)	1.25 (1.18-1.33)	1.00	1.03 (0.87-1.22)	1.14 (1.06-1.23)
			Male			
Person-years of follow-up (per 100,000)	192896	18586	319104	198936	19821	326847
Number of events	1456	167	2246	914	139	1247
Age-standardized rate per 100,000 person-years	552.6	496.4	656.6	324.6	367.8	371.0
Age adjusted RR (95% CI)	1.00	1.19 (1.01-1.41)	1.24 (1.16-1.33)	1.00	1.33 (1.10-1.59)	1.17 (1.07-1.28)
Multivariate adjusted RR (95% CI)	1.00	1.07 (0.91-1.26)	1.28 (1.19-1.37)	1.00	1.08 (0.89-1.30)	1.13 (1.03-1.25)
			Female			
Person-years of follow-up (per 100,000)	484315	3553	70603	493303	3785	72725
Number of events	2332	23	556	1371	17	291
Age-standardized rate per 100,000 person-years	397.1	506.7	565.6	226.2	175.5	287.9
Age adjusted RR (95% CI)	1.00	0.88 (0.59-1.34)	1.20 (1.09-1.32)	1.00	0.94 (0.58-1.53)	1.18 (1.04-1.35)
Multivariate adjusted RR (95% CI)	1.00	0.86 (0.57-1.29)	1.25 (1.13-1.37)	1.00	0.86 (0.53-1.39)	1.19 (1.04-1.36)

*Adjusted for baseline age, sex, education, cigarette smoking, alcohol consumption, physical inactivity, BMI, SBP, geographic region (north vs. south), urbanization (rural vs. urban), cardiovascular disease and the prevalence of diabetes at baseline as well as new onset diabetes during follow-up.

Table 3

Relative risk of stroke in current compared to never smokers according to number of cigarettes smoked per day

	Stroke Incidence					Stroke Mortality				
	Cigarettes per day				P-value for trend	Cigarettes per day				P-value for trend
	0	1-9	10-19	≥20		0	1-9	10-19	≥20	
Total										
Person-years of follow-up (per 100,000)	677210	120541	95702	154798		692239	123469	98507	158695	
Number of events	3788	946	719	1090		2285	602	389	522	
Age-standardized rate per 100,000 person-years	445.1	574.7	619.1	688.6		257.1	352.9	328.1	353.1	
Age and sex adjusted RR (95% CI)	1.00	1.17 (1.09-1.26)	1.19 (1.10-1.29)	1.33 (1.23-1.43)	<0.0001	1.00	1.18 (1.07-1.30)	1.13 (1.01-1.27)	1.16 (1.04-1.28)	0.01
Multivariate adjusted RR* (95% CI)	1.00	1.21 (1.12-1.31)	1.21 (1.11-1.32)	1.36 (1.25-1.47)	<0.0001	1.00	1.15 (1.05-1.27)	1.10 (0.98-1.23)	1.13 (1.02-1.26)	0.06
Male										
Person-years of follow-up (per 100,000)	192896	82806	75027	142875		198936	84813	77048	146357	
Number of events	1456	670	550	981		914	451	297	476	
Age-standardized rate per 100,000 person-years	552.6	614.1	652.0	707.9		324.6	400.2	343.8	371.9	
Age adjusted RR (95% CI)	1.00	1.19 (1.08-1.31)	1.20 (1.09-1.33)	1.34 (1.23-1.46)	<0.0001	1.00	1.22 (1.08-1.37)	1.10 (0.97-1.26)	1.16 (1.04-1.31)	0.05
Multivariate adjusted RR (95% CI)	1.00	1.23 (1.11-1.36)	1.22 (1.11-1.36)	1.37 (1.25-1.50)	<0.0001	1.00	1.17 (1.03-1.32)	1.07 (0.93-1.22)	1.14 (1.01-1.28)	0.15
Female										
Person-years of follow-up (per 100,000)	484315	37735	20675	11923		493303	38656	21460	12339	
Number of events	2332	276	169	109		1371	151	92	46	
Age-standardized rate per 100,000 person-years	397.1	525.1	577.4	645.4		226.2	270.4	340.1	243.9	

	Stroke Incidence					Stroke Mortality				
	Cigarettes per day				P-value for trend	Cigarettes per day				P-value for trend
	0	1-9	10-19	≥20		0	1-9	10-19	≥20	
Age adjusted RR (95% CI)	1.00	1.15 (1.01-1.30)	1.18 (1.00-1.38)	1.36 (1.12-1.65)	0.0003	1.00	1.13 (0.95-1.34)	1.27 (1.02-1.57)	1.15 (0.86-1.55)	0.05
Multivariate adjusted RR (95% CI)	1.00	1.20 (1.05-1.36)	1.21 (1.03-1.42)	1.42 (1.17-1.73)	<0.0001	1.00	1.15 (0.97-1.37)	1.22 (0.98-1.52)	1.18 (0.87-1.59)	0.07

*Adjusted for baseline age, sex, education, cigarette smoking, alcohol consumption, physical inactivity, BMI, SBP, geographic region (north vs. south), urbanization (rural vs. urban), cardiovascular disease and the prevalence of diabetes at baseline as well as new onset diabetes during follow-up.

Table 4

Relative risk of stroke in current compared to never smokers according to pack-years

	Stroke Incidence					Stroke Mortality				
	Pack-years				P-value for trend	Pack-years				P-value for trend
	0	1-11	12-26	>26		0	1-11	12-26	>26	
Total										
Person-years of follow-up (per 100,000)	677210	123913	124469	120442		692239	126364	127600	124400	
Number of events	3788	819	809	1108		2285	496	425	588	
Age-standardized rate per 100,000 person-years	445.1	569.8	648.9	652.4		257.1	343.7	356.0	343.8	
Age and sex adjusted RR (95% CI)	1.00	1.15 (1.06-1.25)	1.21 (1.12-1.32)	1.31 (1.22-1.41)	<0.0001	1.00	1.15 (1.04-1.28)	1.19 (1.06-1.32)	1.17 (1.06-1.29)	0.002
Multivariate adjusted RR* (95% CI)	1.00	1.18 (1.09-1.28)	1.25 (1.15-1.35)	1.34 (1.24-1.44)	<0.0001	1.00	1.13 (1.01-1.25)	1.15 (1.03-1.29)	1.13 (1.02-1.25)	0.02
Male										
Person-years of follow-up (per 100,000)	192896	88765	102833	107606		198936	90426	105173	111061	
Number of events	1456	584	621	984		914	369	333	519	
Age-standardized rate per 100,000 person-years	552.6	600.1	699.7	677.3		324.6	377.5	403.3	358.1	
Age adjusted RR (95% CI)	1.00	1.15 (1.04-1.27)	1.22 (1.11-1.35)	1.35 (1.24-1.46)	<0.0001	1.00	1.15 (1.02-1.31)	1.20 (1.05-1.36)	1.17 (1.05-1.31)	0.009
Multivariate adjusted RR (95% CI)	1.00	1.17 (1.06-1.30)	1.26 (1.14-1.39)	1.37 (1.26-1.50)	<0.0001	1.00	1.11 (0.97-1.27)	1.15 (1.01-1.32)	1.13 (1.01-1.27)	0.05
Female										
Person-years of follow-up (per 100,000)	484315	35148	21636	12836		493303	35938	22427	13339	
Number of events	2332	235	188	124		1371	127	92	69	
Age-standardized rate per 100,000 person-years	397.1	539.4	585.0	516.6		226.2	291.8	250.9	251.8	

	Stroke Incidence					Stroke Mortality				
	Pack-years				P-value for trend	Pack-years				P-value for trend
	0	1-11	12-26	>26		0	1-11	12-26	>26	
Age adjusted RR (95% CI)	1.00	1.19 (1.03-1.36)	1.23 (1.05-1.43)	1.14 (0.95-1.37)	0.0200	1.00	1.19 (0.99-1.43)	1.18 (0.95-1.46)	1.18 (0.92-1.51)	0.08
Multivariate adjusted RR (95% CI)	1.00	1.24 (1.08-1.42)	1.27 (1.09-1.48)	1.18 (0.98-1.42)	0.006	1.00	1.21 (1.01-1.46)	1.16 (0.94-1.45)	1.16 (0.90-1.49)	0.13

*Adjusted for baseline age, sex, education, cigarette smoking, alcohol consumption, physical inactivity, BMI, SBP, geographic region (north vs. south), urbanization (rural vs. urban), cardiovascular disease and the prevalence of diabetes at baseline as well as new onset diabetes during follow-up.